#25
B. Webb
8/3/01

Declaration under 37 CFR § 1.132

We, Dr. Rainer Hintsche and Dr. Manfred Paeschke declare and say:

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1. We are the inventors of the subject matter disclosed in United States application serial number 09/142,660 ("the application").

2. We have reviewed the Office Action that issued from the U.S. Patent and Trademark Office on August 1, 2000. We understand that the U.S. Examiner questions whether the application provides enough information for someone skilled in the art of the invention to practice the invention described in the application ("the present invention") without undue experimentation. We strongly believe that it does for the following reasons:

A. The present invention describes an interdigital transducer, the structure and dimensions of the interdigitating electrodes of which are of about the same or similar size compared to common biological macromolecules. The invention is based on the principle finding that size, charge and fields of biological macromolecules, *e.g.* DNA or proteins, influence and change electrical fields used for detection in the present invention in a very specific and individually differing way. Although the invention is applicable to the detection of all biological macromolecules, it was not necessary to disclose all conditions required for binding the biological molecules to be detected according to the present invention and for forming the respective complexes. This was so because almost every molecule and complex differs from others by its structure and the relationship of its parts to each other part. Thus, for every substance to be measured, the conditions and methods for its preparation are different. However, the issue raised in the Office Action is whether persons skilled in biochemistry are able to easily identify such conditions without undue burden of work. We believe that because all of the requisite variables were well known at the time of the present invention, that the determination of such variables was a matter of routine. *See* Lubert Stryer, "Biochemistry, 3rd ed., Verlag W.H. Freeman & Co., NY 1988, page 7 (Appendix 1).

B. In the application, we use the very common terms "proteins", "nucleic acids", and "haptens" for the definition of the

macromolecules and complexes of molecules useful in the present invention. As a typical example, we describe in the application the formation of a protein complex to a capture molecule bound to the electrodes and its detection. However, there are no difficulties to overcome for forming and detecting other complexes using the method as disclosed for the detection of the exemplified protein complex according to the application. The method using the steps as described in the application may easily be adapted without modification of the procedure of the invention, using parameters and conditions well known in the art and described in documents that were publicly available at the time of the invention. For instance, the procedures using affinity binding and resulting in the complexes of molecules described are part of the basis of the well established and generally used biochemical and medical analyses. They have been worked out and proved to function for all relevant pairs of affinity complexes, *i.e.* protein/protein, protein/hapten, DNA/nucleotid, and RNA/nucleotid. A vast variety of different analytical methods, *e.g.* analytical throw-flow detection, well known since long, optical electrochemical biochip technology and other detection methods use these well known principals of complex formation for the respective specific detection system.

C. We have proved that the principle disclosed in the present invention using a transducer having interdigitated ultramicroelectrodes may be used for the detection of other molecules or molecule complexes without more than the routine knowledge of a person skilled in the art. These molecules or molecule complexes may be detected without undue burden of pre-preparation or requirement of specific knowledge just using the well known principles of affinity binding in biochemistry technology. As employees of Fraunhofer Gesellschaft and working in the Institute of Silicon Technology, we have proved that the present invention can be carried out for the detection of molecules different than those described in the examples in the application in a laboratory, which is not specifically adapted for biochemical technology and where the people are not specially skilled in realizing affinity binding complexes. We have published respective results after the priority date of the present application as mentioned below.

D. For instance, in 1998, we have shown at the "5th World Congress on Biosensors", Berlin, 1998, that the invention made according to the present application enables a skilled person to detect DNA hybridization and differences between "full-matching", "mismatching" and "no-matching" and oligonucleotides using 24-mer oligonucleotide sequences as probes (see Abstract and Protocols in Appendix 1).

Further, we have determined complex formation of ferritin molecules, also in relation to the geometry of the transducer (See Appendix 2 : preprint of M.Paescke, L.M.Buchmann, R.Seitz, R.Hintsche, "Fabrication and investigation of nanometer sized dielectric interdigitated transducers for detection of biomolecular binding" in MICR SYSTEM Technologies 96, eds. H.Reichl, A,Heuberger, VDE Verlag, 1996, p.687 – 692, also published in Dissertation of Manfred Paeschke, University Kiel/Germany 1998, published in "Fortschrittsberichte VDI", 9/274, 1998).

Further, in Example 3 of *et al., International Fair* "Analytika 2000", Munich, April 11, 2000, see Appendix 3 of protocols), where the inventor (R.Hintsche) had reported, that the detection of the tumor marking agent cytokeratin 20 complexed to a respective catching oligonucleotide may be performed with the method disclosed in the present invention without any undue burden. This example also has been performed at our laboratory at Fraunhofer Gesellschaft by E. Nebling.

E. The above examples show clearly and unambiguously that the amount of direction and guidance provided with the present invention is sufficient to use the teaching of the working example for the whole field of very well known biological molecules. Contrary to the Examiner's allegation, **the state of the background art in the field of this invention is very much developed because the present invention incorporates methods that are well known in the art.**

F. We have noticed that the U.S. Patent and Trademark Office ("USPTO") has issued many patents directed to electrical and electrochemical transducers in the field of biosensorics and all of these patents lack detailed descriptions of the biochemical parameters to be met prior to measurement. Therefore, we were in good faith to believe that the USPTO has accepted that sufficient disclosure of a method for the detection of biological molecules does not necessarily encompass detailed description of the parameters of the chemical conditions of the biomolecules to be detected. For example, the following US/PCT applications have been granted:

US 5,672,256:
US 5,653,939 (Hollis, aus ISR der 10698p)
WO 93/22678 (= PCT/US93/03829)
WO 88/09499 (= PCT/US88/01433)

These documents are attached as appendices 5 to 8.

3. All statements made herein of our own knowledge are true and all statements made on information and belief are believed to be true; and further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardise the validity of the application or any document or any registration resulting therefrom.

Date: 05 December 2000

Rainer Hintsche

Date: 20. 12. 2000

Manfred Paeschke

EXHIBIT A